Vascular and Extravascular Volumes of the Kidney of Man

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ABSTRACT

Indicator dilution techniques were used to determine the vascular and extravascular volumes of the normal human kidney. Renal volumes were corrected to 1.73 m² and refer to one kidney. The renal blood volume (V₁₀) averaged 34.8 ± 3.1 ml; the water contained in the distribution volume of labeled inulin (V₁₀ w) averaged 48.8 ± 9.0 ml, and that of tritiated water (VTHO w) 152 ± 20 ml. V₁₀ w was used as an index of the extracellular space of the kidney exclusive of the tubular lumina. VTHO W was interpreted to represent the total exchangeable water content of the kidney. The interstitial volume (AV INT w) and tubular-cellular volume (AV C W) were derived and averaged 27.4 ± 6.2 ml and 93.7 ± 14.3 ml, respectively.

Correction for recirculation by exponential extrapolation was studied and appears satisfactory. Evidence is presented for the existence of significant fluctuations in renal blood flow during the indicator collection intervals, and it is suggested that renal volumes be based on flows determined from the recoveries of each indicator.

ADDITIONAL KEY WORDS indicator dilution studies inulin renal extracellular volume renal blood volume creatinine renal water volume renal blood flow indocyanine green tritiated water

The in vivo measurement of the vascular and extravascular volumes of individual organs has been made possible in recent years by indicator dilution techniques. These measurements are based on the product of blood flows and mean transit times of indicators that gain access to one or more of the aqueous compartments of the organ. With this approach, one of us (F.P.C.) determined the distribution volumes of vascular and extracellular indicators as well as labeled water in the dog kidney (1). In the present study, indicator dilution techniques have been modified to obtain values for these volumes in the normal kidney of man and thus provide a basis for comparison in hypertensive and renal diseases.

Methods

EXPERIMENTAL PROCEDURE

Renal volumes were measured in five normotensive patients (patients 1-5) from the wards of the New York University Medical Divisions of Bellevue Hospital. Their ages ranged from 36 to 44 years; all had blood pressures below 140/90 mm Hg and were considered free of cardiovascular or renal disease. Data concerning blood flow, indicator recirculation, and the mean transit times of inulin and creatinine were obtained in these five subjects as well as in five patients with essential hypertension (patients 6-10), a normotensive patient without renal disease (patient 11), and a normotensive patient with reduced renal function (patient 12). The

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RENAL VOLUMES IN MAN

renal volumes of patients 6-12 are not presented in this paper.

All patients received a regular ward diet, and studies were made when they were fasting but moderately hydrated. Bladder catheterization was done in patients 1-4 and 12, and clearances of inulin (C\text{\text{IN}}) and of para-aminohippurate (C\text{\text{PAH}}) for both kidneys were determined by methods described previously (2, 3). Clearance values were corrected to a surface area of 1.73 m² and were divided by 2 to obtain clearance values for each kidney. Ureteral catheterizations were done in patients 5-11, and the clearances of inulin and PAH of each kidney were determined separately.

Renal artery and vein catheterizations were done according to the method of Seldinger (4). To determine the extent of recirculation, a catheter was also placed in the aorta at the level of the renal artery in patients 1, 6 and 12. The catheter position was determined by fluoroscopic visualization and confirmed by the injection of a small amount of sodium diatrizoate (Hypaque, Winthrop, New York, N. Y.).

Four indicators were used: indocyanine green for the vascular volume, labeled inulin and creatinine as extracellular indicators, and tritiated water as a label of the total exchangeable water content of the kidney. A solution containing .75 to 1.50 mg of indocyanine green (Cardiogreen, Hynson, Wescott & Dunning, Baltimore, Md.) in 0.3 to 0.6 ml of a 0.6% human serum albumin-normal saline solution, 5 μe of inulin-carboxyl-14C (New England Nuclear, Boston, Mass.), 45 mg of creatinine (chromatographically pure, Mann Research Laboratories, New York, N. Y.) and 100 μe of tritiated water (Tritiotope, E. B. Squibb & Sons, New York, N. Y.) was rapidly injected into the renal artery. The volume of injected fluid was 1.5 to 1.8 ml, and the duration of injection was less than 0.5 sec. The injection solution was kept at room temperature and contained a solute concentration of 300 milliosmols/liter. Blood was withdrawn from the renal vein catheter by a Sigmamotor pump at rates between 0.6 and 1.1 ml/sec (Fig. 1). Forty samples of renal venous blood were collected in heparinized tubes resting in a moving rack collector described by Chinard and associates (5) (available from Mr. John Armant, Johns Hopkins School of Medicine, Baltimore, Md.) during an 80-sec period (in patient 12, 40 samtes were collected at intervals of 1 sec). A densitometer (model 103-1R, Guilford Instrument Laboratories, Inc., Oberlin, Ohio) was placed between the venous catheter and the collector as one means of measuring indocyanine green concentrations. The densitometer output was amplified and recorded by a polygraph (Electronics for Medicine, Inc., White Plains, N. Y.). In those studies in which recirculation was monitored, the aortic catheter was directly connected to the collector, and renal venous and aortic blood were simultaneously collected.

Analyses were performed on aliquots of whole blood. Indocyanine green concentrations were determined from the serial blood samples as well as from the densitometer recording (as described above). Samples (0.25 ml) of blood were removed from the collection tubes and diluted in 3.0 ml of a solution containing 0.6 g of human serum albumin in 100 ml of normal saline. Following centrifugation, the supernatant solution was removed and the optical density at 800 μm determined (Spectronic 20, Bausch & Lomb, Rochester, N. Y.). These measurements were made within 8 hours of collection.

The densitometer curves were used to calculate the mean transit time and recovery of indocyanine green because of the better resolution afforded by the continuous recording technique and the shorter catheter delay (Fig. 1). Indicator recirculation and the recovery and mean transit times of inulin, creatinine and tritiated water were calculated from concentrations found in the collection tubes.

Measurements of creatinine and labeled inulin and water were performed on protein-free supernatants. Samples (0.25 ml) of whole blood were diluted in 3.0 ml of water, and 1.67 ml of 10% trichloracetic acid was added to precipitate proteins. The protein-free supernatant, in 0.25 ml portions, was removed and added to 10 ml of a scintillation mixture described by Goresky (6). Quenching remained unchanged during each study and required no correction. Double-label counting was performed in liquid scintillation spectrometers.

Collection and recording apparatus. A more complete description of the blood collector may be found in Chinard and associates (5). Average volume from renal vein to midpoint of densitometer = 1.1 ml. Average volume from renal vein to collection tubes = 4.3 ml. Average withdrawal rate = .85 ml/sec.
Creatinine was determined by a modified Jaffe procedure (7). A volume of 0.6 ml of 0.75 N sodium hydroxide was added to 2 ml of the protein-free supernatant followed by 0.6 ml of 0.04 M picric acid. Thirty minutes after the addition of picric acid, the optical density at 520 m\(\mu\) was measured with a Spectronic 20.

**CALCULATION OF INDICATOR RECOVERIES**

Each indicator concentration was divided by the amount of the indicator injected to obtain "fractional concentrations," \(r_i\), measured in units of \(\text{ml}^{-1}\). This procedure permits comparison of indicator concentration in terms of a common unit, the fraction of the original amount injected present in each milliliter of sample blood (5).

The determination of renal blood flow by the indicator dilution technique is based on the following four assumptions. (1) All of the indicator injected into the renal artery is recoverable in the renal vein. (2) There is no dilution of the renal blood flow by nonrenal blood—e.g. from the inferior vena cava. (3) The renal blood flow and indicator dilution volume remain constant. (4) Complete mixing of indicator with renal blood flow occurs. Under these circumstances, the renal blood flow (\(Q\), in \(\text{ml/sec}\)) may be calculated from the concentration (\(c\), in \(\text{mg/ml}\) or \(\text{cpm/ml}\)) of each sample, the time interval between samples (\(r\), in sec) and the amount injected (\(M\), in \(\text{mg}\) or \(\text{cpm}\)) by the equation

\[
Q = \frac{M}{\sum c r}
\]  

(1)

By converting from \(c\) to \(r\), i.e. by dividing numerator and denominator by \(M\), we obtain

\[
Q = \frac{1}{\sum r T}
\]  

(2)

If indicator is lost before arriving at the vein, the "fractional recovery" (\(f\)) of the injected indicator arriving in the renal vein may be determined from the blood flow by the equation

\[
f = Q(\Sigma r T)
\]  

(3)

The fractional recovery represents the fraction of the injected bolus that would be recovered if all of the venous blood were collected.

The expression (\(\Sigma r T\)) represents the area under the indicator curve and is referred to as the "apparent recovery," designated as \(R\). If a portion of the injection mixture is lost because of reflux into the aorta or if nonrenal blood enters the venous catheter at a constant rate, the loss of an indicator may be determined by comparing its apparent recovery with that of an indicator which is fully recoverable in the renal vein. If it is assumed that indocyanine green (IG) is not lost from the circulation during passage through the kidney (i.e. \(f_{IG} = 1\), this substance may be used as a "reference" indicator to determine the fractional recoveries of other indicators (\(f_i\)):

\[
f_i = \frac{Q\Sigma c T}{Q\Sigma f_{IG} T} = \frac{R_i}{R_{IG}}
\]  

(4)

**VARIATION IN BLOOD FLOW: FLOW CALCULATIONS**

Variation in blood flow (\(Q\)) during the collection interval will invalidate equation 4. Similarly, fluctuation in the quantity of nonrenal blood entering the venous catheter will preclude use of this relationship.

Evidence suggests that renal blood flow does vary significantly during the period of indicator collection (see Appendix). It was therefore necessary to estimate average renal blood flow during intervals approximating the duration of each indicator dilution curve. Accordingly, it was assumed that the fractional recoveries of indocyanine green and tritiated water in the renal venous blood are complete and that the fractional recovery of inulin-carboxy-\(^{14}\)C is complete in the renal venous blood and urine. This assumption represents a departure from the calculation previously used, in which it was assumed that flow is constant and fractional recovery is variable (1). Justification for this procedure is given in the Appendix.

Renal blood flow (\(Q_{IG}\)) during the interval occupied by the indocyanine green curve was calculated from the apparent recovery of indocyanine green. The fractional recovery of indocyanine green was assumed to be complete:

\[
f_{IG} = 1 = Q_{IG} (\Sigma f_{IG} T)
\]  

(5)

The fractional recovery of inulin was assumed to be determined by the fraction lost in the glomerular filtrate (as judged from the inulin clearance and the clearance and extraction of PAH during the concurrent clearance period):

\[
f_{IN} = 1 - \frac{C_{IN} E_{PAH}}{C_{PAH}} = Q_{IN} (\Sigma f_{IN} T)
\]  

(6)

The use of a flow based on the apparent recovery of inulin and the filtration fraction determined during a clearance period is justified by the relatively small effect differences in filtration fraction have on calculated flow. A relatively large error in the filtration fraction will produce a comparatively small error in the calculation of \(Q_{IN}\).
Similarly the fractional recovery of labeled water was considered to be complete, and the renal blood flow during this interval was calculated from the equation

\[ Q_{\text{THO}} = \frac{1}{\sum r_{\text{THO}}} \]

Where \( Q_{\text{THO}} \) represents the renal blood flow, and \( r_{\text{THO}} \) are referred to as "nearest interval flows" (\( Q_{\text{NI}} \)) when used to calculate the distribution volumes of the corresponding indicators.

For comparison, renal blood flow was also calculated from the concomitantly determined clearance (in ml/min) and extraction of PAH.

\[ Q_{\text{PAH}} = \frac{C_{\text{PAH}}}{E_{\text{PAH}} (1 - \text{Hct})} \times 60 \]

RECIRCULATION AND CALCULATION OF MEAN TRANSIT TIMES

The fractional concentrations of indocyanine green were calculated from points selected at 1-sec intervals from the continuous polygraph recording. The fractional concentrations of inulin, creatinine and tritiated water were calculated from the concentrations found in each of the collection samples.

Correction for recirculation was made by assuming exponential washout (8, 9). Fractional concentrations were plotted on a logarithmic scale against time or sample number on a linear scale. The earliest linear downslope was selected and indicator concentrations in excess of this were attributed to recirculation (Figs. 2 and 6).

The recirculation of each indicator to the renal artery was directly determined in three subjects by simultaneously sampling from the renal vein and the aorta at the level of the renal artery. This was done to estimate the contribution made by recirculation to the indicator dilution curves obtained in the renal vein. Comparisons of the exponential extrapolation and aortic concentration were made on linear coordinates (Figs. 3-5).

The mean transit times (\( T \)) were calculated (10) from the equation:

\[ T = \frac{\sum n_d r}{\sum r_c} \]

where \( n \) refers to the ordinal number of the densitometer reading, \( r_c \) designates the fractional concentration corrected for recirculation and \( r_c \) represents the interval between points (1 sec). The fractional concentrations of inulin, creatinine and tritiated water found in the discrete samples were assumed to represent the concentration of each of these indicators at the middle of the collection interval; \( n_d r \) was therefore subtracted from the mean transit times calculated for these substances from equation 9.

The mean transit time of the collection apparatus was determined by dividing the volume of the collector system by the rate of withdrawal of blood during the study. The mean transit times to the densitometer and to the collection tubes were under 1.7 and 6.2 sec, respectively (Fig. 1). The mean transit time through the collection apparatus and one-half the injection duration were subtracted from the mean transit time of each indicator.

CALCULATION OF VOLUMES

Mean transit times obtained by sudden injection techniques may be employed in volume determinations if the injection bolus is adequately mixed in the artery. This has been assumed true in the present study without proof.

The renal blood volume (\( V_{r\text{G}} \)) was calculated in terms of milliliters of blood from the product of the renal blood flow (\( Q_{r\text{G}} \)) and the mean transit time of indocyanine green (\( t_{r\text{G}} \)).

\[ V_{r\text{G}} = Q_{r\text{G}} t_{r\text{G}} \]

The extravascular volumes have been expressed in milliliters of water content rather than plasma equivalents or grams of tissue and differ in formulation from those used elsewhere by Chinard and co-workers (1) and Goresky (6). The following equations were used to calculate each of the renal water volumes:

\[ V_{\text{IGW}} = Q_{\text{IG}} W_{p} \times (1 - \text{Hct}) \]

\[ V_{\text{INW}} = Q_{\text{IN}} (1 - \text{Hct}) W_{p} \times \frac{1}{\text{IN}} \]

\[ V_{\text{INTW}} = V_{\text{INW}} - V_{\text{BW}} \]

\[ V_{\text{THOW}} = Q_{\text{THO}} W_{p} \times \frac{1}{\text{THO}} \]

\[ V_{\text{TOW}} = Q_{\text{THO}} W_{p} \times \frac{1}{\text{THO}} \]

\[ V_{\text{THOW}} = V_{\text{THOW}} - (V_{\text{INTW}} + V_{\text{BW}}) \]

The mean transit time of the collection apparatus was determined by dividing the volume of the collector system by the rate of withdrawal of blood during the study. The mean transit times to the densitometer and to the collection tubes were under 1.7 and 6.2 sec, respectively. The mean transit time through the collection apparatus and one-half the injection duration were subtracted from the mean transit time of each indicator.
Renal Clearances and Description of Patients

### TABLE 1

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>S.A. (m²)</th>
<th>Hct</th>
<th>Urine Flow* (ml/min)</th>
<th>C(IN)* (ml/min)</th>
<th>Cl'AI* (ml/min)</th>
<th>FF</th>
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<td>464</td>
<td>.213</td>
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<tr>
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<td>.168</td>
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<td>(left)</td>
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<td></td>
<td>2.85</td>
<td>45.5</td>
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<td>.164</td>
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</table>

*Values of patients 1-4 pertain to both kidneys; those of patient 5 pertain only to the left kidney. Two clearance periods were obtained during the indicator studies of the fifth patient.

Fractional volume of water in red blood cells was similarly estimated from the product of the fractional mass of water in red blood cells (.72) (Altman) and the specific gravity of red cells (1.099) (Altman) to be .791. \( W_B \) designates the fractional volume of water in whole blood and was calculated from the fractional volume of water in red cells and plasma and the hematocrit by means of the equation

\[
W_B = .791 \text{ Hct} + .966 (1 - \text{Hct}).
\]  

The values for \( V_{10}, V_{IN}^W, \Delta V_{INT}^W, \Delta V_C^W \) and \( V_{THW}^W \) are given in Table 3. Other quantities discussed in this communication can be calculated from these data.

In order to compare relative volumes obtained in the present study with those obtained by Chinard and co-workers (1) in the dog, mean transit time ratios have been calculated from both sets of data. The ratios \( t_{TN}/t_{20}, t_{15}/t_{1}, t_{THO}/t_{15} \) and \( t_{TN}/t_{1} \) will be influenced by catheter position, since both numerator and denominator of each fraction will contain a constant related to

![Figure 2](image1)

**Figure 2**

Appearance of indocyanine green, inulin-carboxyl-\( ^{14} \)C and tritiated water in the renal vein following injection in the renal artery (patient 1, first study). Semilogarithmic plot with exponential extrapolations (straight lines). Uncorrected for catheter delay. \( \tau = 2 \) sec.

![Figure 3](image2)

**Figure 3**

Appearance of indocyanine green in renal vein and aorta following injection in the renal artery (patient 1, first study). Exponential extrapolation is indicated by dotted line. Uncorrected for catheter delay. \( \tau = 2 \) sec.

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the transit time through the impermeable portions of the renal vascular bed. This error may be eliminated by subtracting the vascular transit time from numerator and denominator; the ratio \( \frac{t_{IN} - t_{IG}}{t_{THO} - t_{IG}} \) eliminates errors from this source. These ratios will not, however, yield volume ratios if renal blood flow varies during the collection intervals.

**Results**

The inulin and PAH clearances \( (C_{IN}, C_{PAH}) \), PAH extraction \( (E_{PAH}) \), hematocrit \( (Het) \) and urine flow present at the time of the volume determinations are indicated in Table 1. In the first four patients, the clearances of one kidney were estimated from bladder collections by dividing the total clearances by 2; in the fifth, ureteral collections were obtained.

**Indicator Curves and Correction for Recirculation**

In Figure 2, the fractional concentrations \( (r) \) of indocyanine green, labeled inulin, and tritiated water found in the serial collection samples are plotted on a semilogarithmic scale against tube number \( (n) \) for a typical study (patient 1, first study). Correction for catheter delay is not indicated in these curves. The exponential extrapolation of each curve is indicated by straight lines. It can be seen that extrapolation is readily obtained for indocyanine green and inulin but is somewhat less certain for tritiated water.

Figures 3-5 show simultaneous venous and aortic concentrations of each indicator in the same study on linear coordinates. The exponential extrapolation is shown with dotted lines. No more than 15%, and usually significantly less, of the total recovery was eliminated by extrapolation during intervals approximating the major portion of the indicator curves. Arterial concentrations of indocyanine green, labeled inulin, and tritiated water re-
FIGURE 6
Densitometer recording of indocyanine green concentration in the renal vein following injection in the renal artery (patient 1, first study). The initial small rise is an artifact.

mained less than 4%, 6% and 15%, respectively, of the maximum renal venous concentrations of these indicators. Both the fraction of the indicator curve removed by exponential extrapolation and the quantity returning to the renal artery are small, suggesting that the former procedure is acceptable for correcting the curves for recirculation.2

The continuous indocyanine green curve recorded from the densitometer during the same study is shown in Figure 6. Minor fluctuations imposed by the peristaltic withdrawal pump are evident. Fractional concentrations obtained from this curve at 1-sec intervals have been plotted in Figure 7 on semilogarithmic coordinates, and a linear extrapolation has been drawn.

RENNAL BLOOD FLOWS AND APPARENT RECOVERY RATIOS

Table 2 gives the renal blood flows measured by PAH (QPAH) and each indicator (QIG, QIN, QTHO). Of the four methods of determining blood flow, QIG tended to yield the lowest values. In all but two runs, QIG was less than QPAH and in all but three runs QIG was less than QIN and QTHO. No consistent difference was observed between QPAH, QIN and QTHO.

These results do not necessarily imply that the washout of indicator is a first-order logarithmic function. Gomez (12) has obtained a close fit to the indocyanine green curve with a beta function.

The apparent recovery ratios are indicated in the second section of the table: RIN/RIG = .75 ± .05, RTHO/RIG = .91 ± .09. Both ratios varied between studies and between individual subjects. Since the indicator flows (QIG, QIN, QTHO) have been calculated from the indicator recoveries (RIG, RIN, RTHO), relationships observed between the indicator flows reflect the recovery ratios. The average apparent recovery of inulin (RIN/RIG) was somewhat less than that anticipated from clearance data (1 - CIN/CAPA = .83). Similarly, the apparent recovery of water (RTHO/RIG) was usually less than unity. These observations are responsible for the finding that QIG is less than QIN or QTHO.

In the third portion of the table, the indicator mean transit times are shown.

RENAL VOLUMES AND RENAL VOLUME RATIOS

The renal volumes as calculated from the nearest interval flows (QNI) are indicated in the last section of Table 2. These data pertain to one kidney and have been corrected to 1.73 m² body surface area. The mean and
<table>
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<th>Patient</th>
<th>( Q_{VAH} ) (ml/sec)</th>
<th>( Q_{II} ) (ml/sec)</th>
<th>( Q_{IN} ) (ml/sec)</th>
<th>( R_{IN} )</th>
<th>( R_{THI} )</th>
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<th>( t_{IN} ) (sec)</th>
<th>( t_{THI} ) (sec)</th>
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<td>6.16</td>
<td>6.12</td>
<td>.89</td>
<td>1.04</td>
<td>5.52</td>
<td>12.5</td>
<td>26.1</td>
<td>35.1</td>
<td>47.6</td>
<td>144</td>
<td>25.9</td>
<td>86.8</td>
</tr>
<tr>
<td>8.5</td>
<td>8.12</td>
<td>7.16</td>
<td>7.19</td>
<td>.98</td>
<td>1.13</td>
<td>4.55</td>
<td>10.4</td>
<td>23.0</td>
<td>37.0</td>
<td>46.2</td>
<td>149</td>
<td>23.4</td>
<td>92.5</td>
</tr>
</tbody>
</table>

*Calculated from nearest interval flows.
†\( Q_{II} \) technically unsatisfactory.
‡Average of first and third runs.
TABLE 3

Indicator Dilution Volumes Calculated from $Q^*_{SP}$, $Q^*_{PAH}$ and $Q^*_{IG}$

<table>
<thead>
<tr>
<th></th>
<th>$V_{IO}$ (ml)</th>
<th>$V_{IN}$ (ml)</th>
<th>$V_{THIO}$ (ml)</th>
<th>$V_{INT}$ (ml)</th>
<th>$V_{CN}$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{NI}$</td>
<td>Mean</td>
<td>34.8</td>
<td>48.8</td>
<td>152</td>
<td>27.4</td>
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<tr>
<td></td>
<td>sd</td>
<td>±3.1</td>
<td>±9.0</td>
<td>±20</td>
<td>±6.2</td>
</tr>
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<td></td>
<td>Variance</td>
<td>7.3</td>
<td>9.5±</td>
<td>58</td>
<td>9.5</td>
</tr>
<tr>
<td>$Q_{PAH}$</td>
<td>Mean</td>
<td>39.7</td>
<td>48.5</td>
<td>153</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>sd</td>
<td>±5.6</td>
<td>±9.2</td>
<td>±25</td>
<td>±4.7</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>24.4</td>
<td>30.3</td>
<td>155</td>
<td>34.4</td>
</tr>
<tr>
<td>$Q_{IG}$</td>
<td>Mean</td>
<td>34.8</td>
<td>44.4</td>
<td>138</td>
<td>34.4</td>
</tr>
<tr>
<td></td>
<td>sd</td>
<td>±3.1</td>
<td>±8.0</td>
<td>±28</td>
<td>±5.9</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>7.3</td>
<td>24.4</td>
<td>268</td>
<td></td>
</tr>
</tbody>
</table>

*Same five patients as in Tables 1 and 2.
†Upper values have been calculated from all of the volumes; lower values exclude the fourth run of patient 3.

Discussion

The renal blood volume of these five patients averaged $34.8 \pm 3.4$ ml. This is in good agreement with the renal blood volume reported by this laboratory in an earlier study (36.7 $\pm$ 10.9 ml) (13, 14), using a somewhat different system of collection and calculation. Other investigators (15, 16) have found that the mean transit time of plasma protein labels

![Diagram showing concentration of creatinine and inulin-carboxyl-14C over time.](http://circres.ahajournals.org/)

FIGURE 8

Appearance of inulin-carboxyl-14C and creatinine in the renal vein following injection in the renal artery (patient 1, first study). Uncorrected for catheter delay. $r = 2$ sec.

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standard deviation for each volume are given in Table 3. The following mean transit time ratios were calculated: $t_{IN}/t_{IO}$ averaged $2.05 \pm 1.11$; $t_{THIO}/t_{IO}$ averaged $4.52 \pm 56$; and $(t_{X} - t_{IO})/(t_{THIO} - t_{IO})$ averaged $0.332 \pm 0.072$.

For purposes of comparison, the average volumes and standard deviations calculated from $Q^*_{PAH}$ and $Q^*_{IG}$ are also shown (lower portion of Table 3). The variance in volumes between studies in individual subjects is indicated for each technique. Although the average volumes calculated by each technique were comparable, use of the nearest interval flows consistently yielded the lowest variance. Among these five patients, the differences between variances of volumes calculated by each technique were significant at a 5% level only for $V_{THIO}$, where $Q^*_{NI}$ (i.e. $Q^*_{THIO}$) yielded significantly less variation than $Q^*_{NI}$.

The transit time curves of two "extracellular" substances, inulin and creatinine, were compared in two normotensive patients (1, 3) and four hypertensive patients (7-10). Figure 8 shows a comparison of these substances in a typical study (patient 1, first study). The ratio of the mean transit time of inulin to the mean transit time of creatinine ($t_{IN}/t_{IO}$) averaged $0.333 \pm 0.027$ in this group. This ratio should represent the ratio of the indicator volumes since the duration and shape of the inulin and creatinine curves were similar, and renal blood flows were therefore presumably equal.
RENAL VOLUMES IN MAN

in dogs is slightly greater than that of labeled red cells. Chinard and co-workers (16) observed that the renal volume of distribution of labeled red blood cells is about 16% smaller than the simultaneously obtained volume of distribution of protein labels in dogs. It is presumed that plasma protein labels enter a larger volume than do red blood cells, but it is not yet clear whether this additional volume is within the vessels or outside of them. Another variable factor is the loss of fluid from the glomerular capillaries, which will produce a rise in indocyanine green concentration in the initial portion of the postglomerular circulation. This rise in concentration will prolong the mean transit time of indocyanine green and will result in a modest exaggeration of the calculated vascular volume.

The inulin water volume of the kidney averaged 48.8 ± 9.0 ml. The space of distribution of inulin was first used by Gaudino and Levitt (17) as a measure of the extracellular volume of the whole body. Inulin characteristically becomes distributed in a smaller volume than other extracellular indicators. Measurements of the extracellular volume of dogs averaged 19.4% of the total body weight in contrast to 30.4% for 24Na and 33.8% for NaSCN. Similarly, Chinard and co-workers (1) found that the mean transit time of inulin through the canine kidney is slightly shorter than that of creatinine and several other extracellular indicators that shared a common volume (t_{IN}/t_{CR} = .901). It was suggested that this may be due either to delayed passage of inulin molecules through the capillary wall or complete exclusion from a portion of the extracellular space (the "excluded volume" phenomenon) (18) as a consequence of the large size of the inulin molecule. In this study, the inulin volume averaged 93% of the creatinine volume in two normotensive and four hypertensive patients (t_{IN}/t_{CR} = .933 ± .027). Although the volume calculated from the mean transit time of inulin may be somewhat smaller than the true extracellular volume, the inulin volume may be proportional to the renal extracellular volume in man. Since that portion of the injected inulin entering the tubules is not recovered in the renal venous blood, the tubular luminal volume is not included in this measurement. It is assumed that the mean transit time of inulin recovered in the renal vein is not influenced by loss in the glomerular filtrate.

The ratio of the mean transit time of inulin to the mean transit time of indocyanine green (t_{IN}/t_{IG}) averaged 2.05 ± .11. Values of 1.73, 1.76, 1.56, and 1.50 were calculated for t_{IN}/t_{IG} from four studies reported by Chinard and co-workers (1) in anesthetized dogs (lower values were found in animals with reduced hematocrits).

The ratio of the mean transit time of labeled water to that of indocyanine green (t_{IN}/t_{IG}) averaged 4.52 ± .56. This was greater than the comparable average calculated from data obtained by Chinard and co-workers (1) in the dog (3.36). (t_{IN} - t_{IG}/t_{IN} - t_{IG}) averaged .332 ± .072 in the present study. The differences of the mean transit time ratios between the two studies may be due to differences of experimental conditions (catheter placement was performed by an open surgical approach with general anesthesia in the animal studies) or to species differences.

Each of the volumes determined in this study provides a measure of compartmental volume exchanging during the 80 sec of blood collection. It is to be expected that slowly exchanging regions such as the renal medulla

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are excluded in these studies. Differences in renal volumes in individual subjects noted in this series may indicate real differences in compartment size or may result from alterations in tissue perfusion or exchange. It is unlikely that a very great portion of the total water volume is excluded, since fair agreement with autopsy data has been obtained.

Appendix

The renal volumes reported in this study were based on the mean transit times and recoveries of each indicator. The selection of individual indicator recoveries to measure renal blood flow was prompted by several observations indicating that, under the conditions of this study, renal blood flow might vary significantly during the time intervals required for the recovery of each indicator.

The failure to obtain equal "apparent recoveries" of indocyanine green and tritiated water from the renal vein and labeled inulin from the renal vein and glomerular filtrate has been attributed to variation in blood flow rather than indicator loss. The tendency for blood flow calculated from the recovery of indocyanine green to be less than that calculated from the recoveries of labeled inulin or water or the clearance and extraction of PAH suggests that the intraarterial injection of indicators may occasionally produce a transient decline in renal blood flow. The loss of as much as 20% of the tritiated water label observed in this and earlier studies (1) is unlikely. Losses of labeled water in the urine, lymph and papilla should not exceed 5% of the total label entering the organ. The absence of a significant difference between $Q_{PAH}$, $Q_{IN}$ and $Q_{THO}$ suggests that tritiated water and labeled inulin are fully recoverable.

Although discrepancies in indicator recoveries may arise from extrapolation of the indicator curves, errors from this source are probably not significant since both the correction for recirculation used and the actual return of indicator to the renal artery are relatively small. A significant admixture of nonrenal venous blood also appears improbable since the extraction of PAH found in each of these studies was relatively complete (.81 to .90) and in good agreement with previous studies.

To assess rapid alterations in renal blood flow, three continuous infusion studies were performed in two normotensive subjects (5, 11) and one continuous infusion study in each of two hypertensive subjects (7, 10). Densitometer recordings were obtained of blood drawn from the renal vein by a Harvard Pump or by the collection apparatus (described above) during continuous infusions of indocyanine green. Portions of four densitometer recordings from each of the normotensive subjects are shown in Figure 9. Blood flow was calculated by the variable flow equation suggested by Cropp and Barton (23). Average renal blood flow was compared during intervals of 10 to 16 sec and 44 to 52 sec (approximately equivalent to the intervals required for obtaining 90% of the indocyanine green and tritiated water curves of these subjects). Average flow varied as much as 20% between these intervals.

If flow is variable, measurement of both flow and mean transit time will necessarily be approximate (24), but the use of flows measured concomitantly with mean transit times appears warranted. The observation that volumes determined with nearest interval flows are less variable in individual subjects under control circumstances than those calculated from a single flow determination, e.g., $Q_{IG}$ or $Q_{PAH}$, lends additional support to the contention that flow is variable and better calculated from each indicator recovery.

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